9 April 1999

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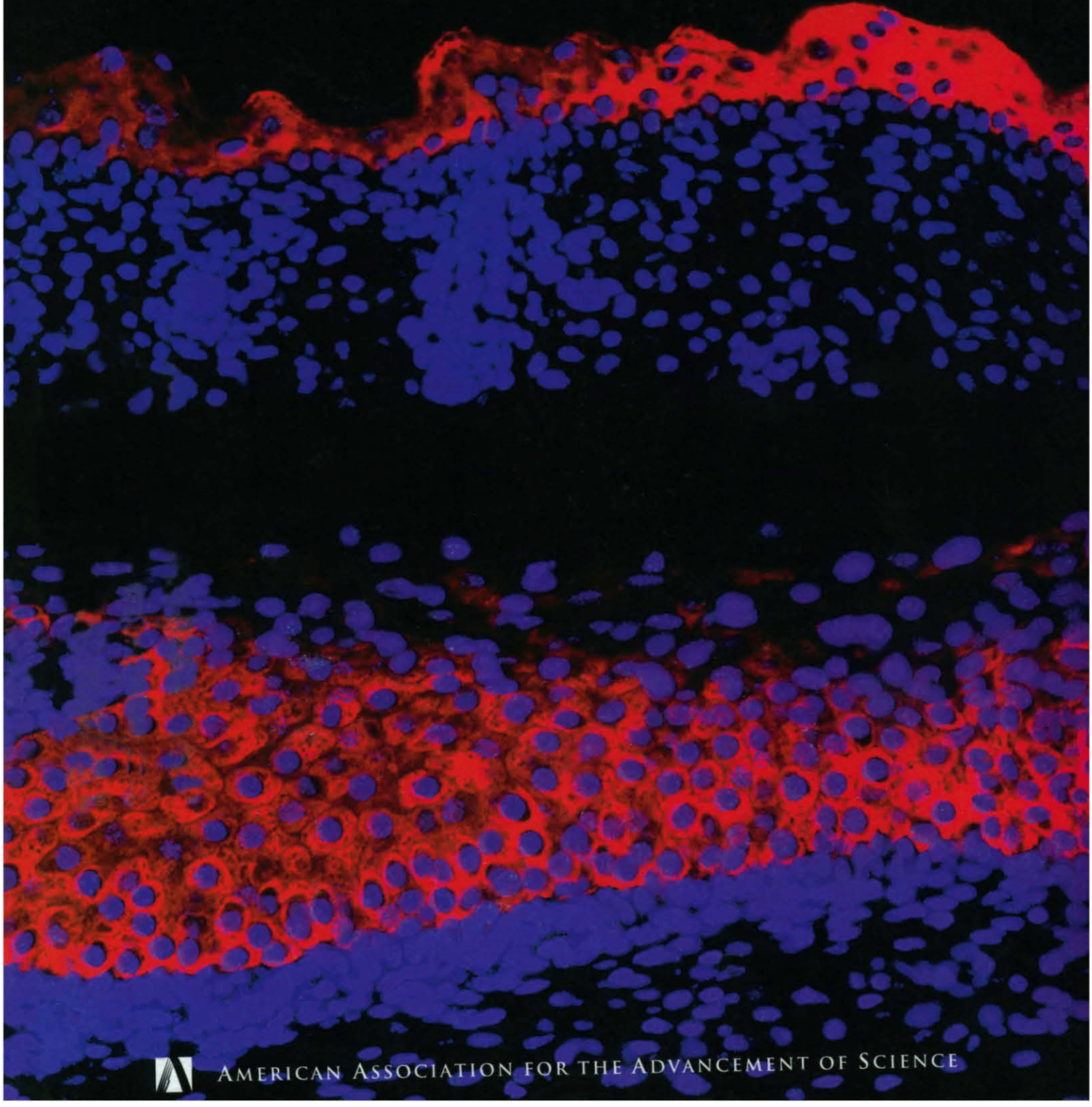

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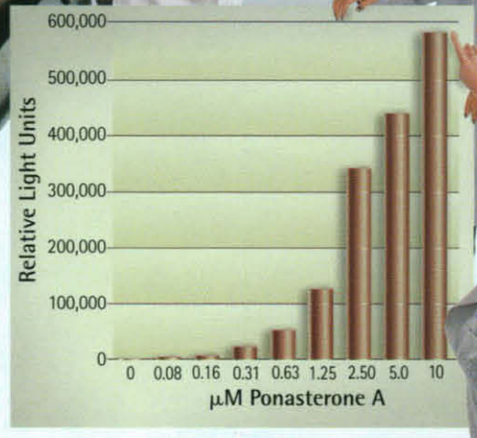

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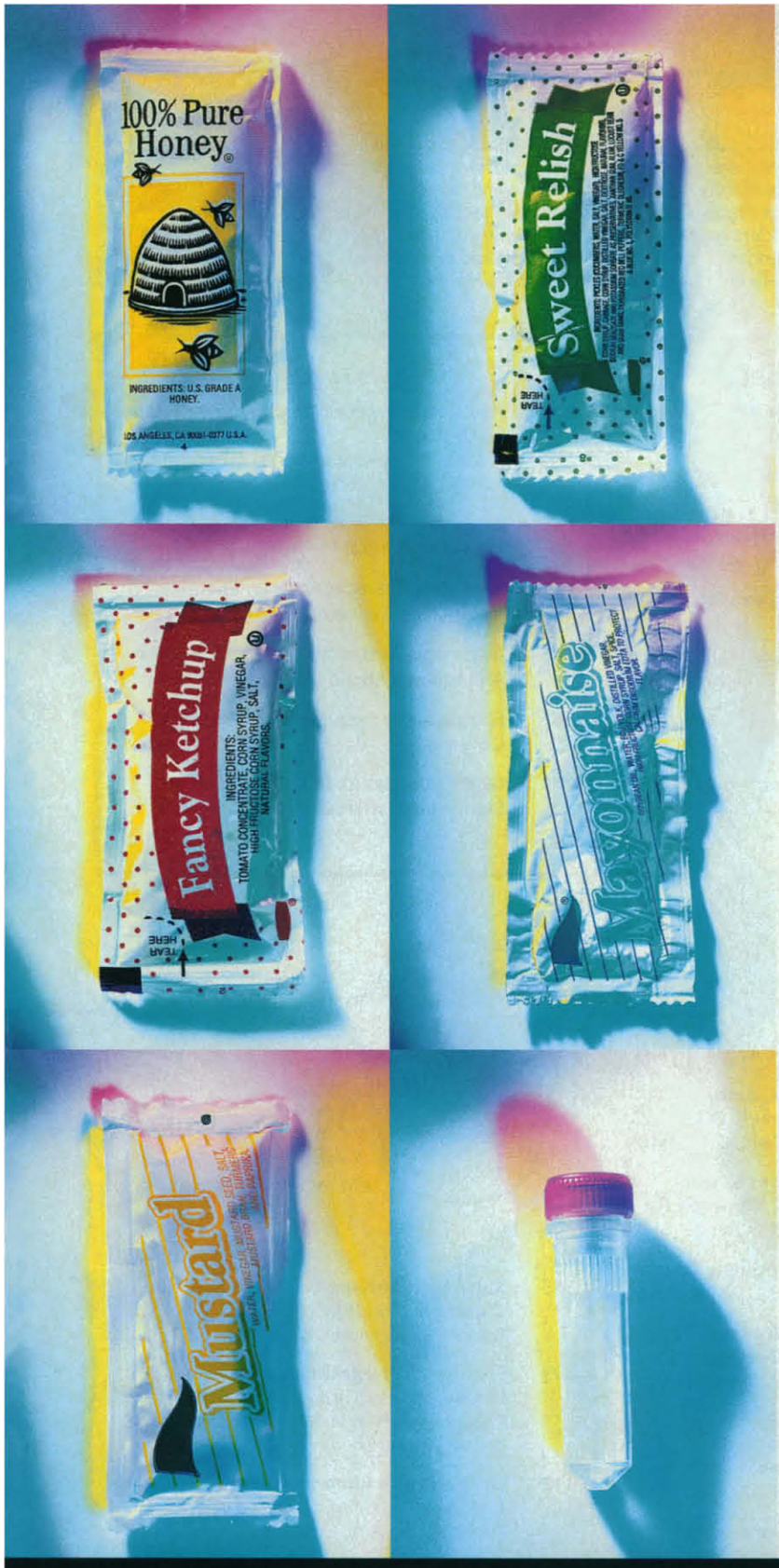

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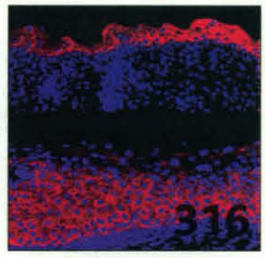

COVER The IκB kinase (IKK) complex is responsible for triggering inflammatory responses. However, gene ablation expriments have identified an unexpected function for the IKKα subunit of this complex—control of epidermis formation. Sections of epidermis (~30 μm tall) from normal (top) and IKKα-deficient mice (bottom) stained to visualize nuclei (purple) and nondifferentiated cells (red) reveal the marked expansion of nondifferentiated cells in mutant epidermis. [Image: Y. L. Hu]

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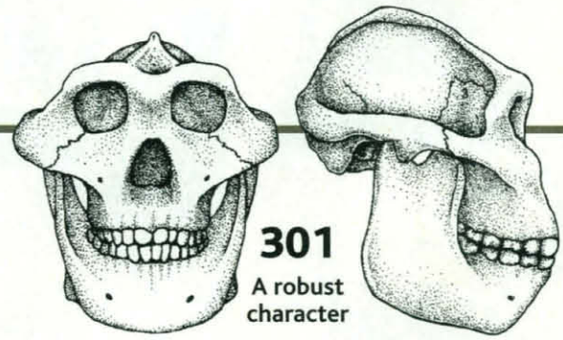
Arctic climate oscillator

NEWS

NEWS OF THE WEEK

NEWS FOCUS

RESEARCH



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A robust character

REPORTS

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Sustaining common-pool resources

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A cooler route to ceramics

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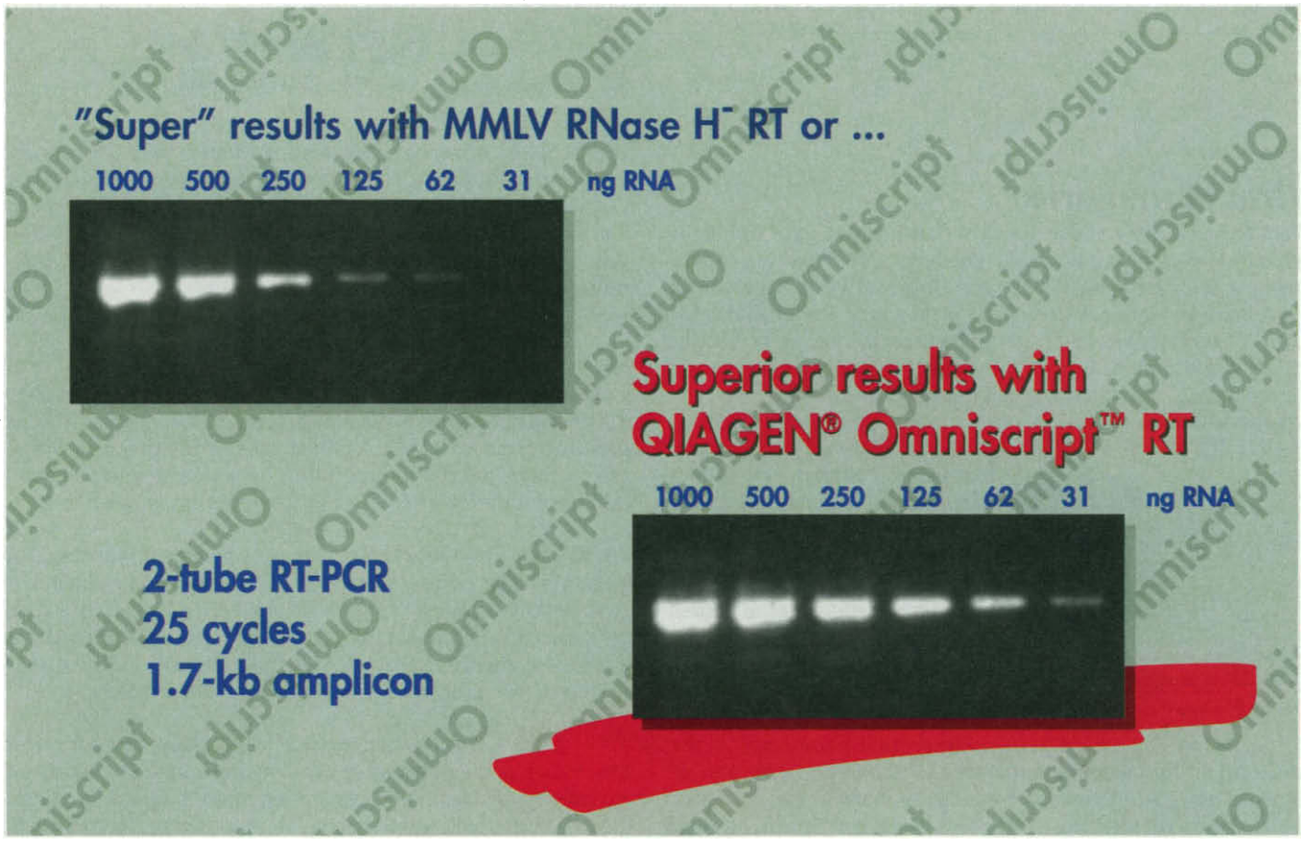

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TINY SWITCH

As the demand for faster computers with larger memory grows, there is a need to reduce the size of the devices that perform logic operations. However, the extent to which the dimensions of transistors can be reduced and operate conventionally is limited by leakage currents. One approach for creating nanometer-scale devices is to make use of properties other than charge. Amlani *et al.* (p. 289; see the Perspective by Smith) demonstrate one such approach based on quantum-dot cellular automata, in which polarization and not charge determines the state of the device. Logical AND and OR gates were fabricated whose state at very low temperatures was determined by the position of just two electrons.

DON'T CROWD THE FERMIONS

Particles that obey Bose-Einstein statistics (such as photons) can occupy the same energy level—bosons like to be together. More than 40 years ago, Hanbury Brown and Twiss demonstrated experimentally one of the fundamental properties of these particles: When they are emitted from a thermal boson source, they do so in bunches (see the Perspective by Büttiker). Henny *et al.* (p. 296) and Oliver *et al.* (p. 299) now verify in two different and independent experiments that, in contrast to the bosons, particles obeying Fermi-Dirac statistics (such as electrons) exhibit antibunching. This behavior was predicted theoretically, but up to now had evaded experimental verification.

COOLER CERAMIC SYNTHESIS

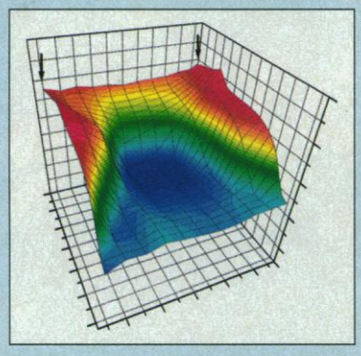
For many device applications, single-crystal films or materials are favored because the grain boundaries of polycrystalline materials adversely effect their properties. Switzer *et al.* (p. 293) show that electrochemical methods can produce single-crystal films of cubic bismuth oxide at room temperature on gold substrates. This material, which has excellent ion transport properties for fuel cell applications, is normally unstable below 730° Celsius and is formed as a kinetically stabilized product.

ABOUT FACE

Hominid phylogenies are defined in many cases by differences in characters of the face and cranium (the most commonly preserved and diagnostic fossils). McCollum (p. 301; see the news story by Morell) examines, for the case of the robust australopithecines (an enigmatic group of hominid fossils), the degree to which many of these characters can be attributed to relatively simple changes in dental proportions that have a developmental basis. Thus, the cladistic "definition" of this group may not be indicative of the phylogeny.

WAVING IN THE DISTANCE

When waves are triggered in a medium—by throwing stones in a pond or sending electrical impulses to the heart—they usually emanate from the point of stimulation. Christoph *et al.* (p. 289) describe an electrochemical system where triggering initiates a



wave at a point distant from the trigger. The oxidation of formic acid at platinum electrodes has passive (OH^- poisoned) and active (high current) states, and an appropriate voltage pulse can initiate two circularly traveling wave fronts that activate the passive state. However, a pulse of an opposite sign, which might be expected to reinforce the passive state, instead initiated activation waves but from a point opposite the trigger pulse. Such action at a distance occurs because the coupling function for ion migration that allows wave propagation reverses its sign at longer distances.

SOLAR CASCADE

Several climate indices and environmental or ecological phenomena show an approximate 11-year cycle that seems to be similar to the solar cycle. However, the irradiance change associated with the solar cycle is very weak, so it has been very difficult to demonstrate a mechanistic connection. Shindell *et al.* (p. 305; see the news story by Kerr) now show, using a climate model that includes ozone variability and wavelength-dependent irradiance, that the solar cycle may have an effect on tropospheric climate. The connection is that changes in stratospheric ozone abundance, driven by the solar irradiance cycle, may affect stratospheric circulation, which affects tropospheric energy and thus regional surface temperatures.

LEAVING THE FOLD

Protein structures usually react to single mutations by relatively small adjustments in their structure; significant changes to secondary and tertiary structural elements are generally believed to require more severe sequence changes, such as large insertions or deletions. Cordes *et al.* (p. 325) show that in the small Arc repressor protein dimer, a switch between just two residues results in a local change from a β-sheet to a helical structure. Within the constraints imposed by the connectivity between the secondary structure elements, such a change can be understood from the sequence pattern. Even relatively small numbers of mutations can thus alter a protein fold.

CONTROLLING NF-κB

The activity of NF-κB, a master transcription factor for many genes essential for inflammatory and immune responses, is held in check by inhibitory proteins known as IκBs. In cells exposed to tumor necrosis factor (TNF) or interleukin-1 (IL-1), IκBs are phosphorylated and degraded. The phosphorylation of IκBs is thought to be mediated by IκB kinase complexes that include similar IKKα and IKKβ (or IKK1 and IKK2) protein kinase subunits. Four reports, which describe the phenotypes of mice that lack either IKKα or IKKβ, provide new insight into the physiological roles of these enzymes. Li *et al.* (p. 321) show that cells from mice lacking IKKβ indeed have reductions in the responsiveness of NF-κB to TNF and IL-1. The mice themselves die before birth because of increased apoptosis in the liver. Loss of IKKα, however, produced a quite distinct phenotype. Hu *et al.* (p. 316) and Takeda *et al.* (p. 313) find that these mice die shortly after birth and show abnormalities in proliferation and development of skin and in morphogenesis of the limbs and skeleton. In cells from mice lacking IKKβ, activation of NF-κB in response to TNF and IL-1 remained intact. Delhase *et al.* (p. 309) provide additional evidence that IKKα is the enzyme that mediates signaling from TNF-α and IL-1

CONTINUED ON PAGE 223

from an analysis of mutant forms of the IKKs that lack sites for activation by phosphorylation. Furthermore, their results indicate that IKKβ may be inactivated through autophosphorylation of a cluster of serine residues at the carboxyl terminus of the protein, thus limiting the duration of inflammatory signaling. In a Perspective, May and Ghosh outline the current understanding of the signaling mechanisms that control activity of NF-κB in light of the findings that define distinct biological roles for IKKβ.

BALANCING NUTRITION

Plant seeds contain stored protein, lipid, and starch in various combinations that contribute to that seed's value as a food or oil source. Lin *et al.* (p. 328) identified a protein, SSE1, in the small oilseed plant *Arabidopsis*, and found that mutations in SSE1 can disrupt the storage of protein and lipid in favor of starch. Thus, the diverse metabolic pathways that assemble the storage materials are intricately interlinked, and the ultimate balance of components may be amenable to readjustment.

DADS AND DAUGHTERS

In mammals, although each parent contributes genetic material to its offspring, parent-specific genomic imprinting allows for the favored expression of one parent's allelic contribution over the other. Li *et al.* (p. 330) examined the imprinted mouse gene *Peg3*. Although this gene is expressed exclusively from the paternal allele, it is responsible for regulating maternal behavior, nurturing, and growth of the offspring. Mutation of *Peg3* yielded a decreased level of oxytocin neurons. Because oxytocin has been shown previously to affect maternal nurturing and lactation, the regulation of maternal behavior by the paternally expressed gene *Peg3* is now better understood physiologically.

PATTERNS IN NATURE

Harte *et al.* (p. 334; see the Perspective by Rosenzweig) examine the properties of self-similar populations and communities. They demonstrate that several fundamental ecological generalities—the species-area curve, the species-abundance distribution, and a new area-endemism relation—can be linked conceptually into a single framework. The work also shows that two widely accepted patterns—the lognormal species-abundance distribution and the power-law species-area curve—conflict with one another.

INJURIOUS IONS

The role that ions play in cell death is the subject of two reports. During stroke, neurons are thought to die in part because of the overactivity of the NMDA class of neurotransmitter receptors. These receptors form channels for a variety of ions, including potassium. Yu *et al.* (p. 336) explored the hypothesis that potassium efflux from cells may contribute to their demise. Under conditions that mimic those found in stroke, cultured neurons were found to undergo apoptosis in response to NMDA-receptor–mediated potassium efflux. One of the classic examples of cells dying an apoptotic death is by calcium influx into neurons, which activates a phosphatase called calcineurin. How calcineurin evokes death has not been clear. Now Wang *et al.* (p. 339) report that calcineurin can associate with and remove an inhibitory phosphate from the pro-apoptotic protein BAD. This process relocates BAD from the cytosol of the neurons into the mitochondria, where it dimerizes with and inactivates the anti-apoptotic protein Bcl-x_L. Thus, brain insults and conditions that increase Ca^{2+} can modulate the phosphorylation state of a key protein in the apoptosis pathway.

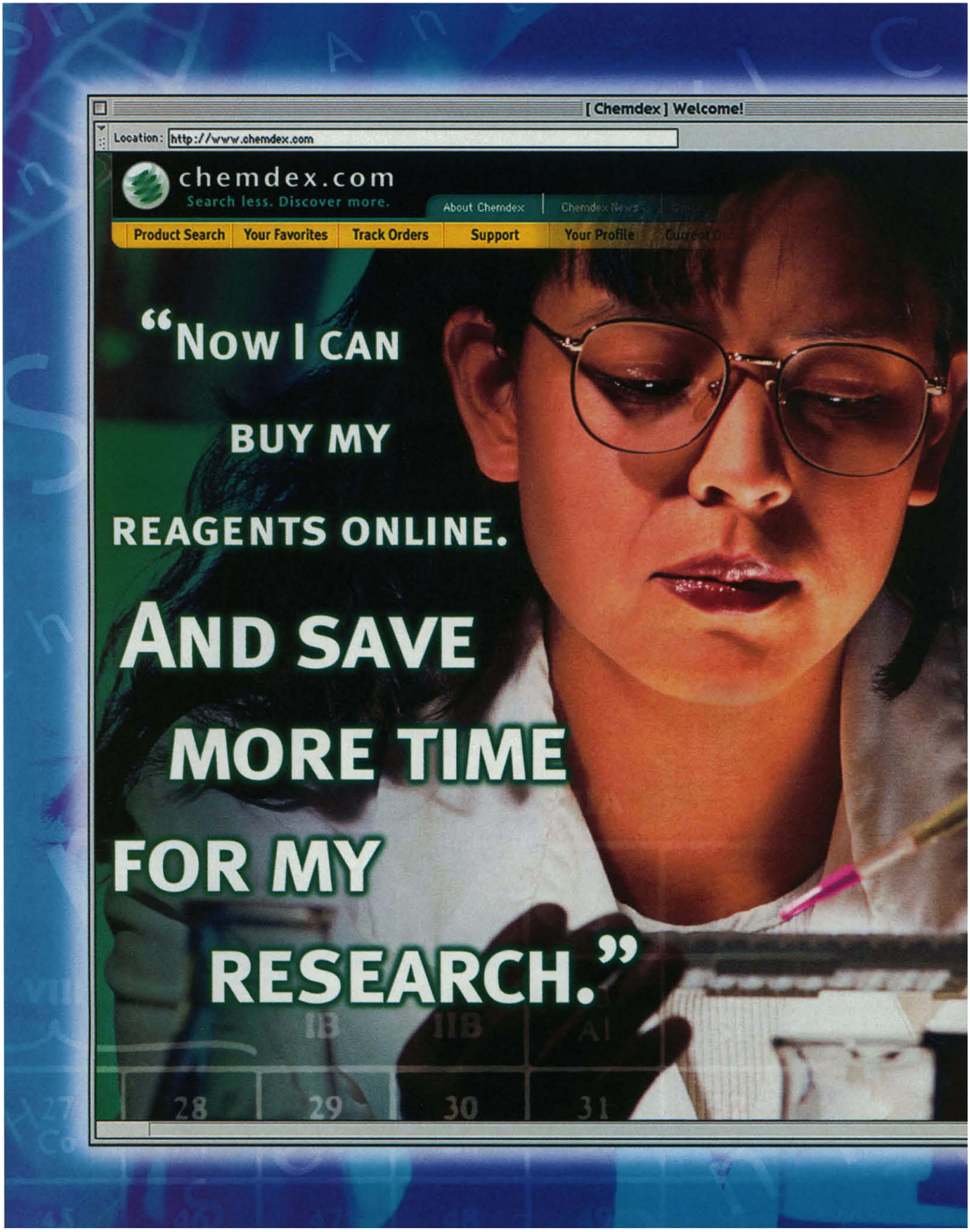
TECHNICAL COMMENT SUMMARIES

The full text of these comments can be seen at www.sciencemag.org/cgi/content/full/284/5412/223a

CCR5 Promoter Alleles and Specific DNA Binding Factors

M. P. Martin *et al.* (Reports, 4 Dec., p. 1907) performed "genetic association analysis of five cohorts of people with acquired immunodeficiency syndrome (AIDS) [which] revealed that infected individuals homozygous for a multisite haplotype of the *CCR5* regulatory region containing the promoter allele, *CCR5P1*, progress to AIDS more rapidly than those with other *CCR5* promoter genotypes, particularly in the early years after infection."

J. H. Bream *et al.* (including several co-authors of the original report) comment that they "have found a distinction in specific binding affinity for separate *CCR5P* allele sequence motifs to nuclear binding (potential transcription) factors, which suggests a possible mechanism for *CCR5P1/P1* epidemiologic consequences."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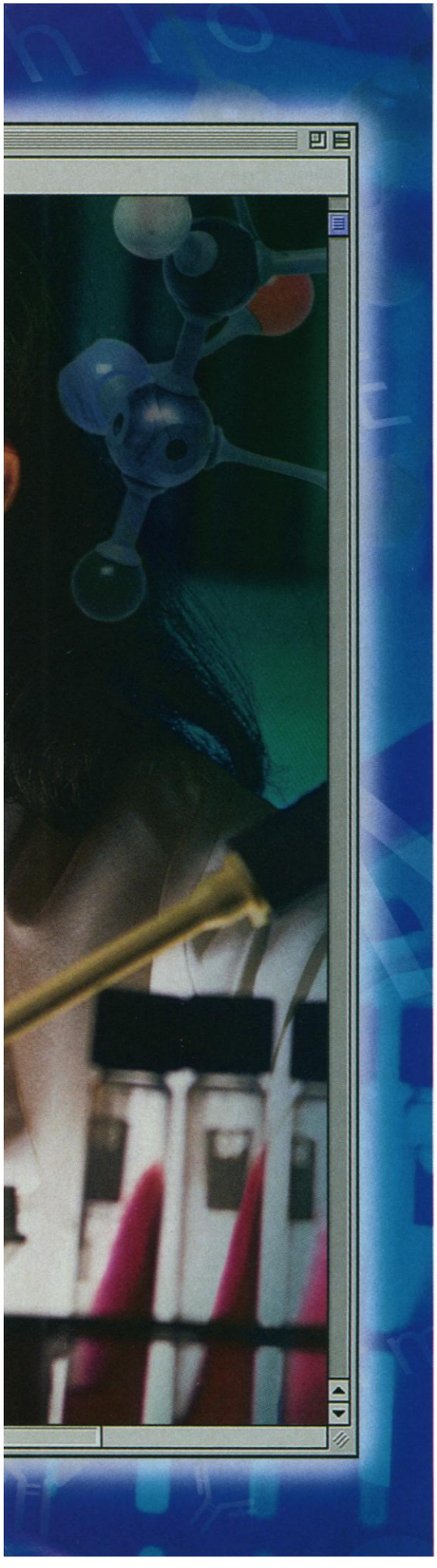

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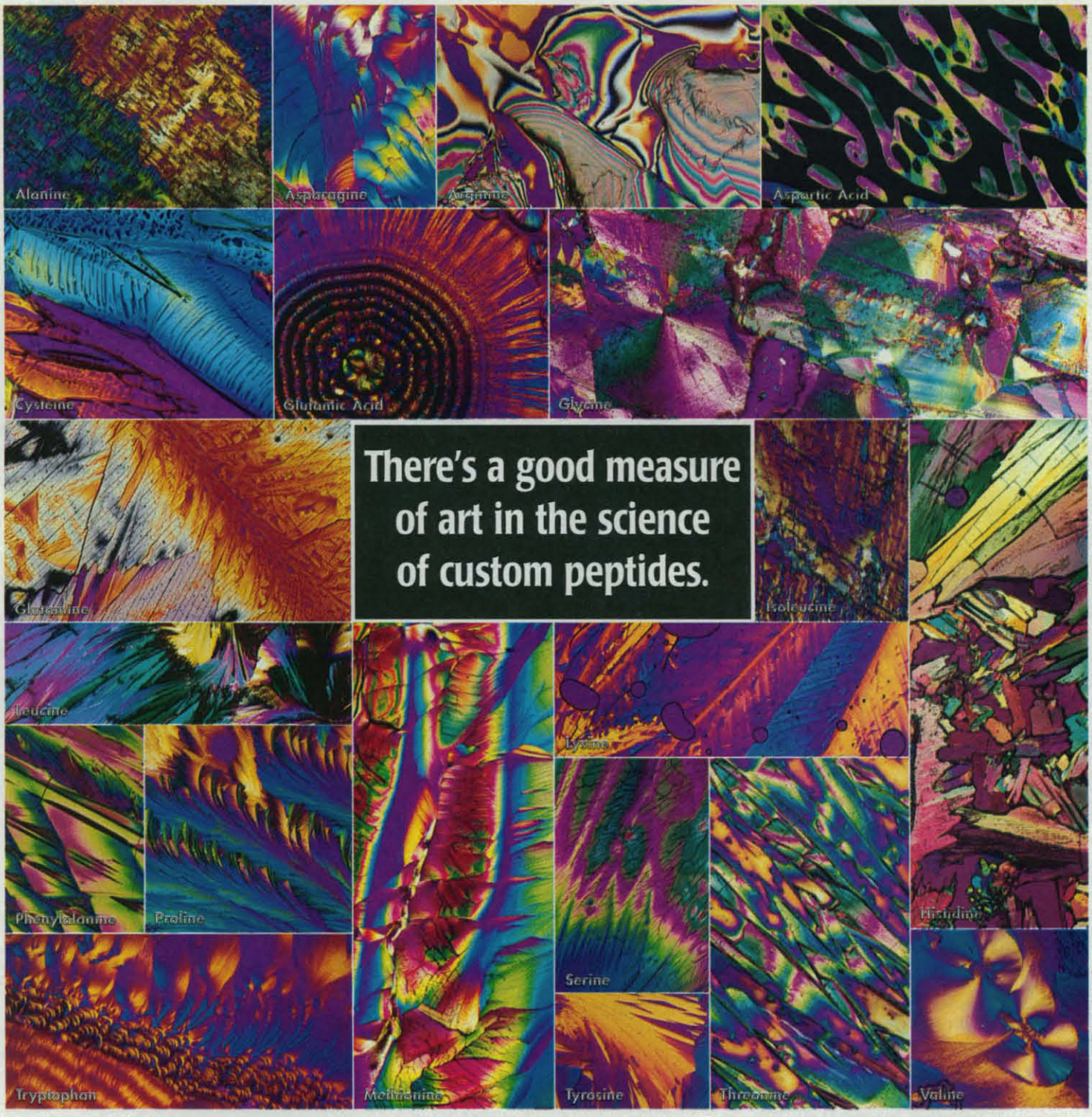

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"AUTOMATION IN THREAT REDUCTION AND INFECTIOUS DISEASE RESEARCH: NEEDS AND NEW DIRECTIONS"

APRIL 29-30, 1999

THE NATIONAL ACADEMY OF SCIENCES AUDITORIUM, WASHINGTON, DC

Organizers Kumar Patel, Tony J. Beugelsdijk, Scott P. Layne

DESCRIPTION

To make headway in many problems in medicine and biology requires enormous quantities of laboratory-based data. The limiting factor often is the fact that humans, unaided, are not capable of generating such vast inventories of data. Today, for the first time, various scientific disciplines and powerful technologies can be brought together to level the playing field against a number of the important problems facing society.

The scientific side of the Colloquium will focus on the needs for measuring, detecting, and monitoring in areas such as: 1) recognizing and addressing established and emerging infectious diseases; 2) ensuring a safe food supply; 3) averting catastrophic bioterrorism and biowarfare; and 4) advancing human genetics and molecular medicine. The technological side of the Colloquium will focus on the various automation, robotic, computer, information, Internet, and microscale laboratory technologies that are available for supporting such scientific needs. The objective is to identify specific scientific needs, assess current research practices and their limitations, and then consider strategic ways for integrating new high-throughput laboratory tools and technologies.

• **Infectious Diseases.** As we move into the 21st century, infectious diseases will pose formidable challenges from a variety of directions. The Colloquium will therefore consider scientific needs for such infectious diseases as influenza, tuberculosis, HIV/AIDS, and other drug-resistant infections; and routes toward developing high-throughput laboratory resources that can accelerate basic science, clinical trials, and public health/epidemiology investigations throughout the world.

• **Food Supply.** Pathogenic food-borne infections are increasing in the U.S. and elsewhere, demanding stringent public health monitoring. The Colloquium will consider scientific needs for protecting the food supply and environment, and ways to engineer high-throughput laboratory resources for improving public health efforts.

• **Biowarfare and Bioterrorism.** The malicious release of hazardous infectious agents poses significant threats to national and global security. The Colloquium will consider the needs for conventional laboratory automation and the development and integration of newer microscale technologies for carrying out a broad range of activities.

• **Further Applications.** The Colloquium encourages participation and interest from a widespread scientific constituency. Its multidisciplinary approach entails broad-based participation from academic, governmental, and industrial sectors.

In addition, the two-day program of presentations and panel discussions has an educational component that should be of interest to policy makers. In order to facilitate tangible outcomes from the Colloquium, a "cross-cutting" approach will be emphasized. This approach recognizes that new tools and technologies from one scientific discipline can be carried over to others, and that the synthesis will result in synergy.

REGISTRATION FEE $200 (non-refundable/can be transferred) includes meals (dinner on April 29th) and one copy of Colloquium proceedings. Accommodations are self-arranged by attendees.

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SPEAKERS

INTRODUCTION

Kumar Patel, University of California, Los Angeles, CA

INFECTIOUS DISEASES

Roy M. Anderson, *University of Oxford, Oxford, UK*
Nancy J. Cox, *Centers for Disease Control and Prevention, Atlanta, GA*
James M. Hughes, *Centers for Disease Control and Prevention, Atlanta, GA*
Scott P. Layne, *University of California, Los Angeles, CA*
Gary J. Nabel, *University of Michigan, Ann Arbor, MI*
Peter L. Nara, *Biological Mimetics Inc., Frederick, MD*
Ariel Pablos-Mendez, *Columbia College of Physicians, New York, NY*
Gary K. Schoolnik, *Stanford University, Palo Alto, CA*
Jeffery K. Taubenberger, *Armed Forces Institute of Pathology, Washington, DC*

FOOD SUPPLY

John C. Bailar III, *University of Chicago, Chicago, IL*
Joseph Rodricks, *Life Sciences Consultancy, Washington, DC*
Bala Swaminathan, *Centers for Disease Control and Prevention, Atlanta, GA*

BIOWARFARE AND BIOTERRORISM

Ken Alibek, *Battelle Memorial Institute, Alexandria, VA*
Ashton B. Carter, *Harvard University, Cambridge, MA*
Donald Kerr, *Federal Bureau of Investigation, Washington, DC*
Gerald Parker, *U.S. Army Medical Research Inst. of Infectious Diseases, Frederick, MD*
William C. Patrick III, *BioThreats Assessment, Frederick, MD*

FURTHER APPLICATIONS

Russell J. Howard, *Maxygen Inc., Redwood City, CA*
Leena Peltonen, *University of California, Los Angeles, CA*
David J. Galas, *Keck Graduate Institute of Applied Life Sciences, Claremont, CA*
J. Craig Venter, *Celera Genomics, Rockville, MD*

TECHNOLOGIES

George A. Bekey, *University of Southern California, Los Angeles, CA*
Tony J. Beugelsdijk, *Los Alamos National Laboratory, Los Alamos, NM*
James H. Jett, *Los Alamos National Laboratory, Los Alamos, NM*
Gary W. Kramer, *National Institute of Standards and Technology, Gaithersburg, MD*
David J. Lipman, *National Library of Medicine, Bethesda, MD*
Thomas Marr, *Genomica Corporation, Boulder, CO*
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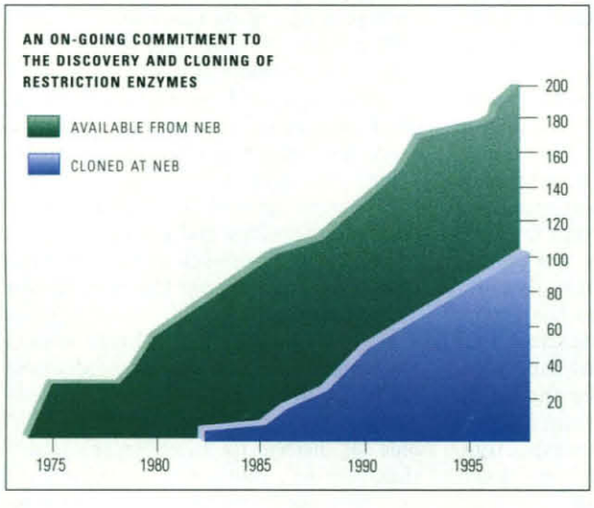

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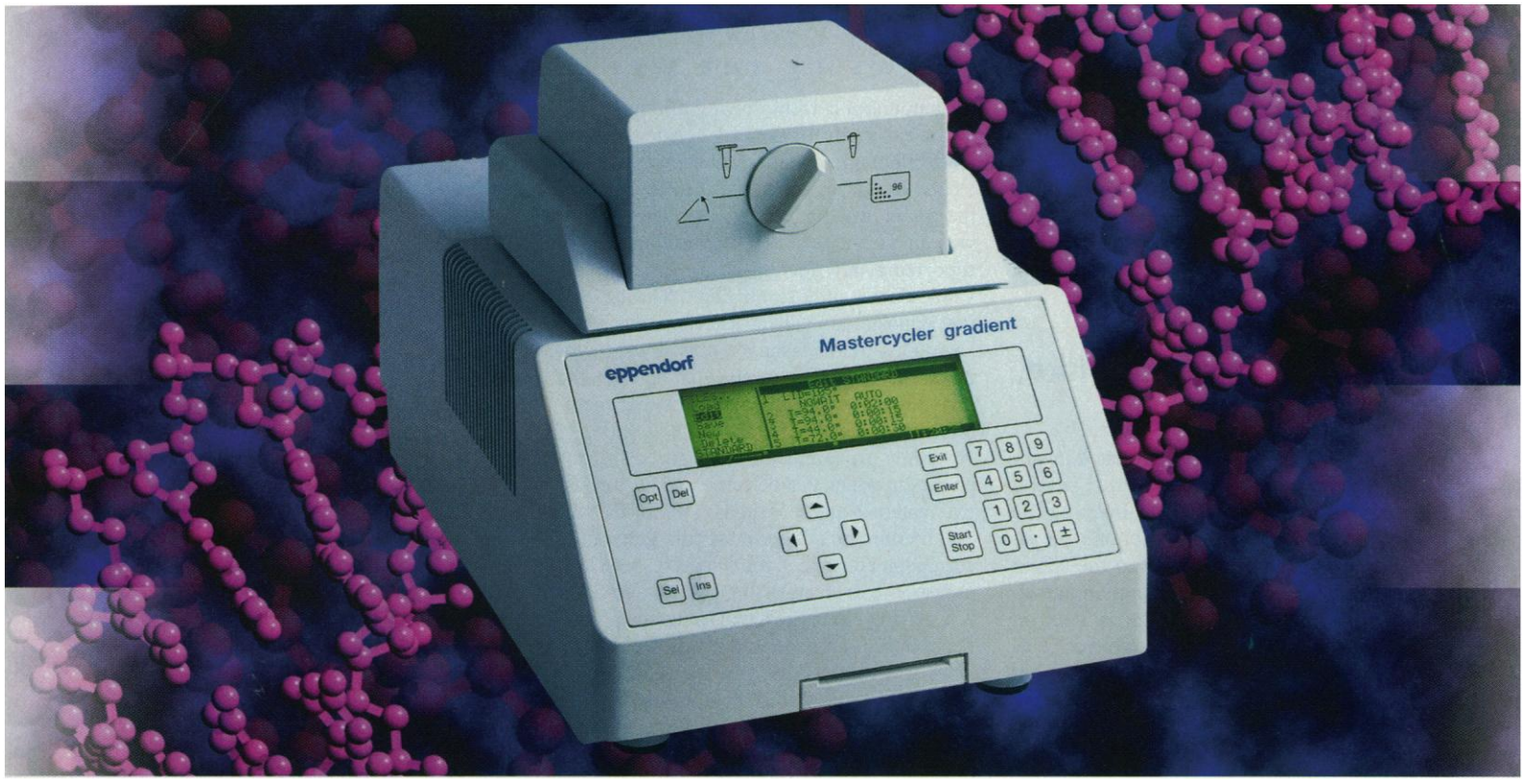

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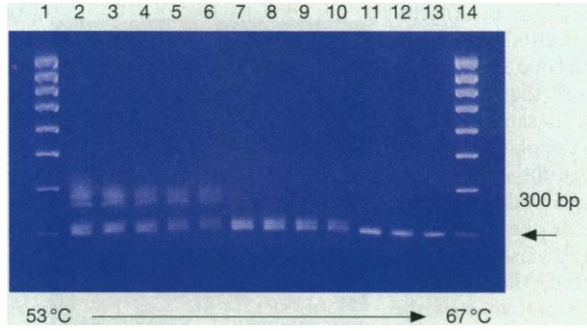

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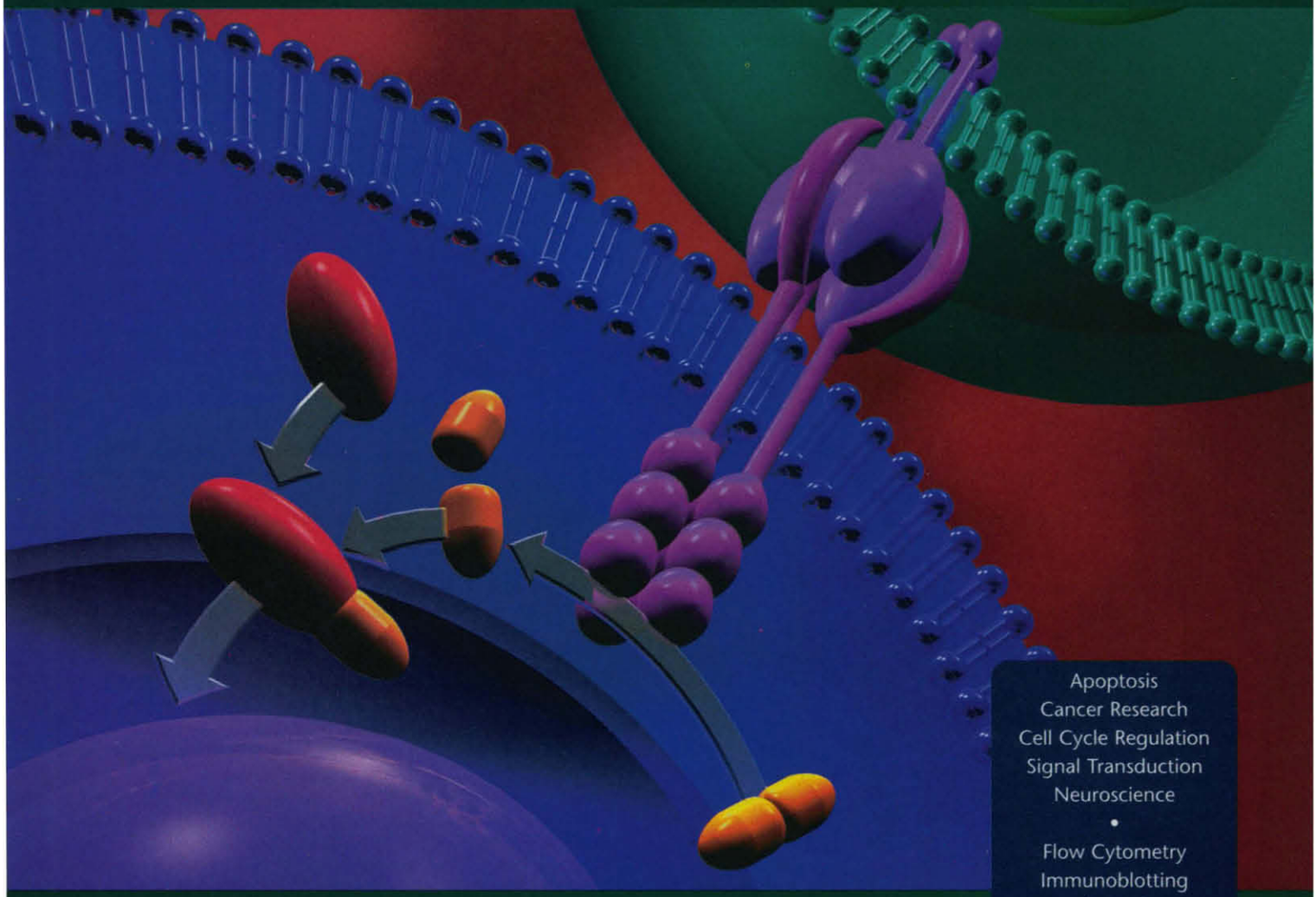

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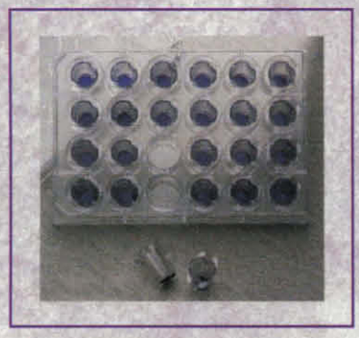

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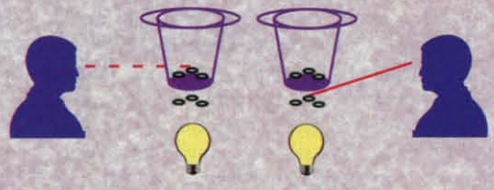

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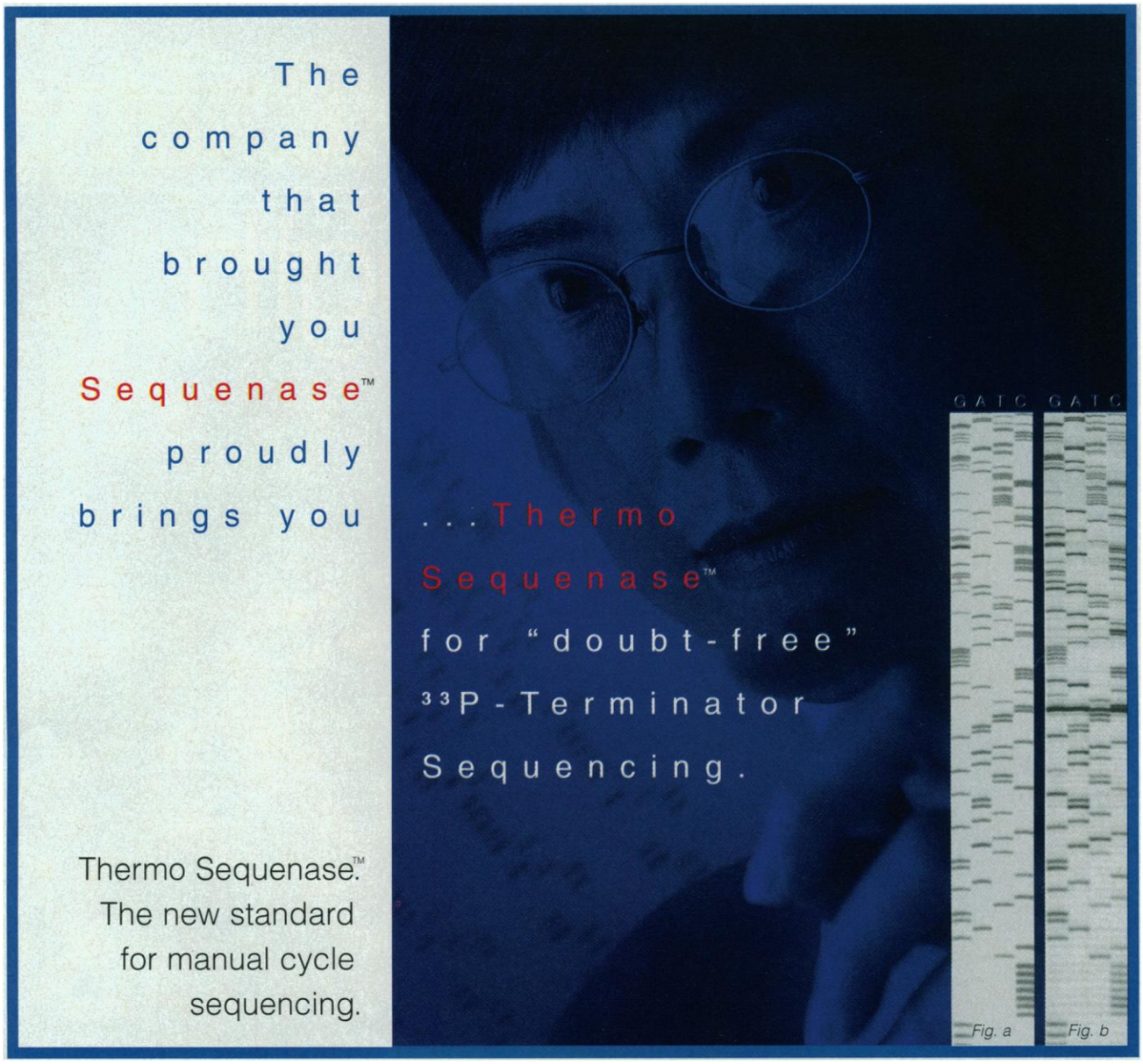

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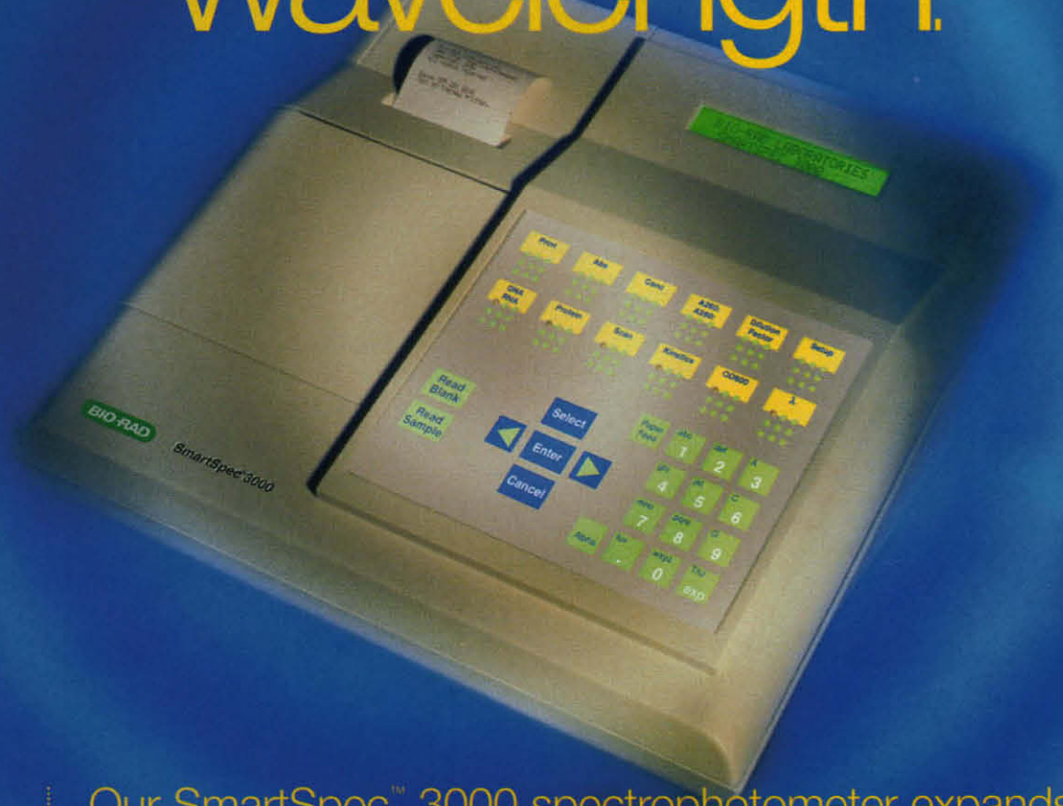

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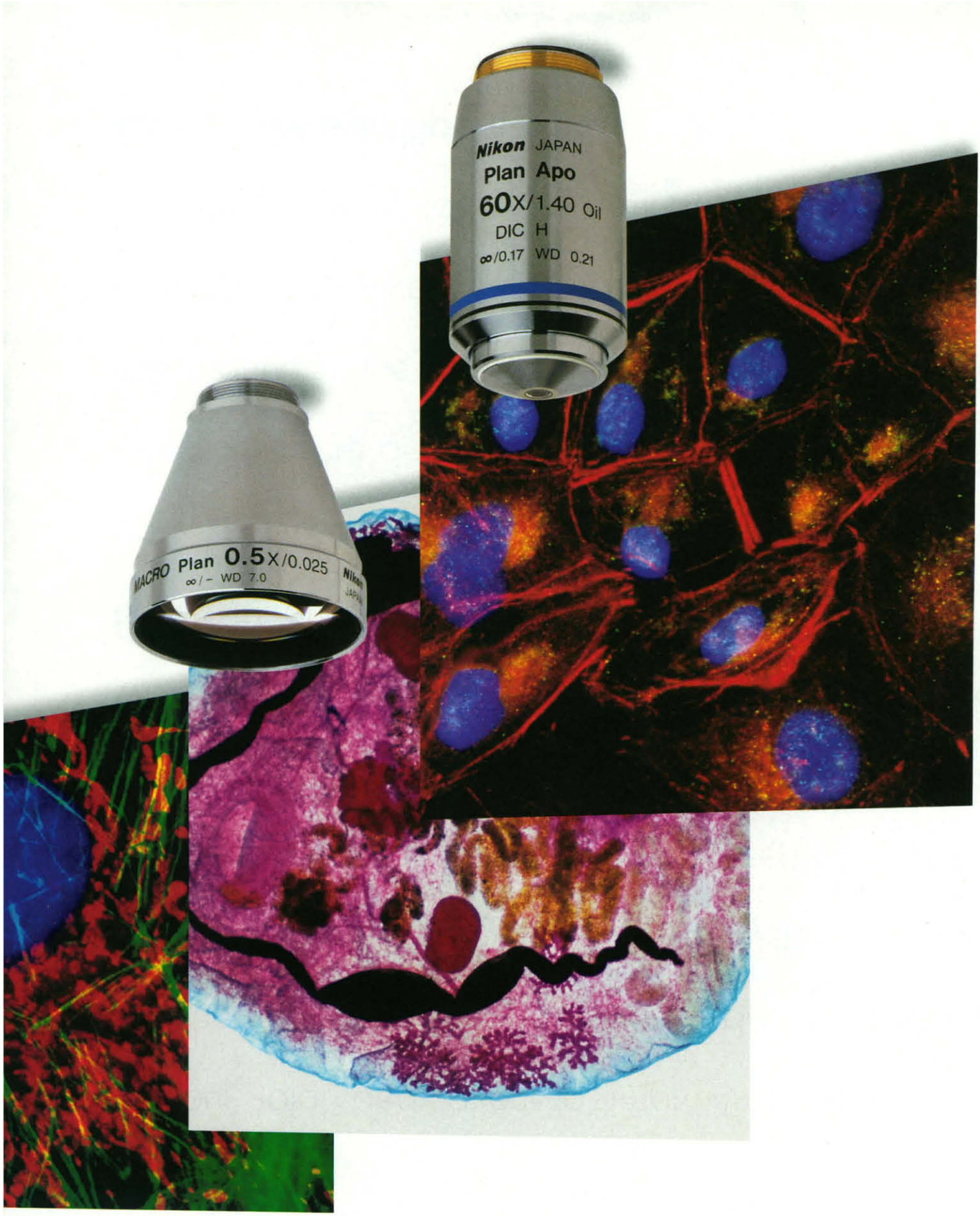
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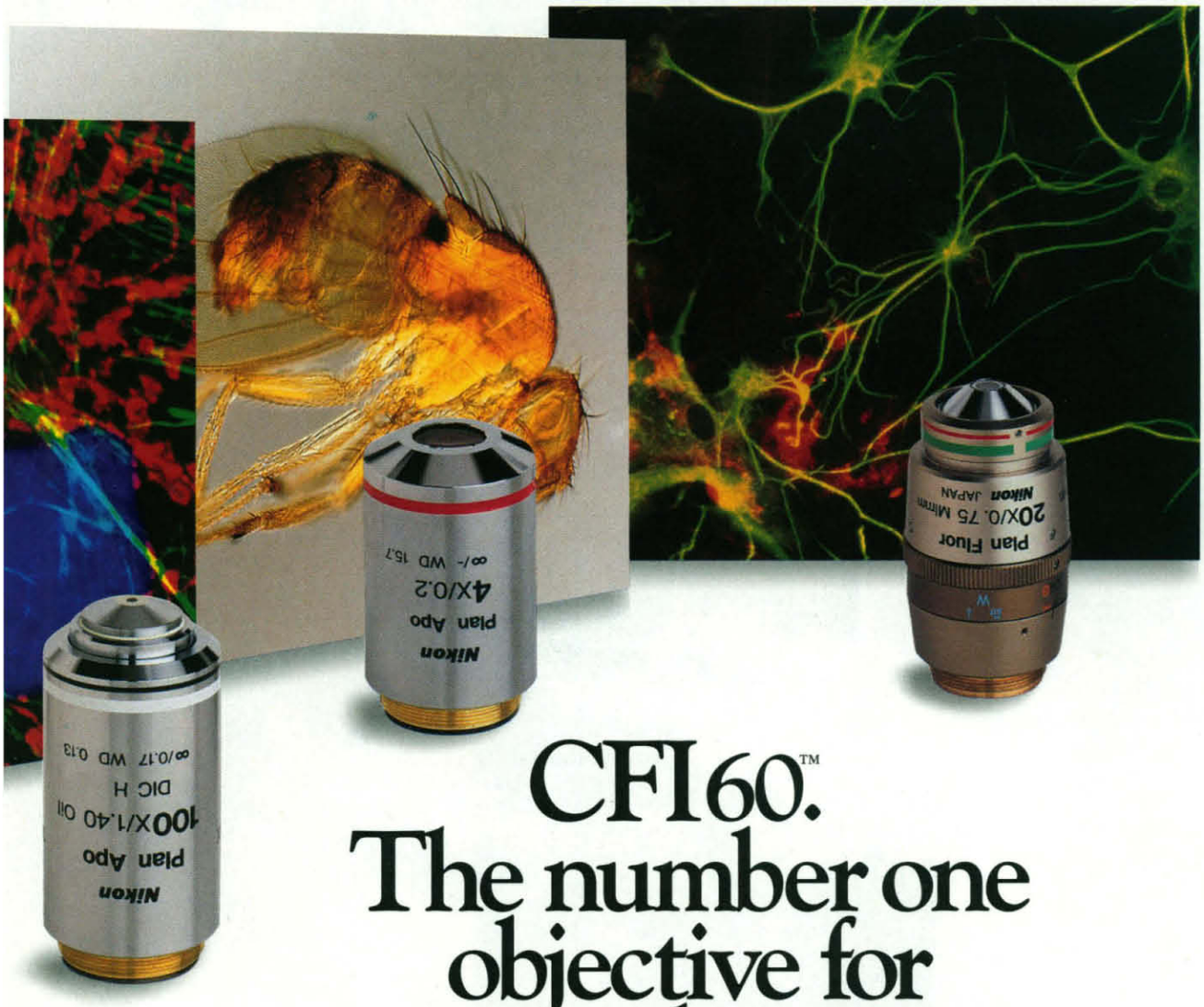

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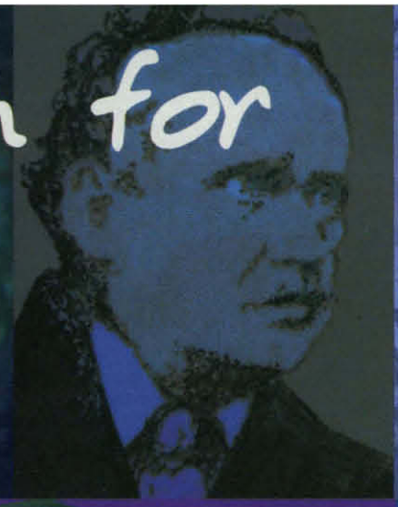

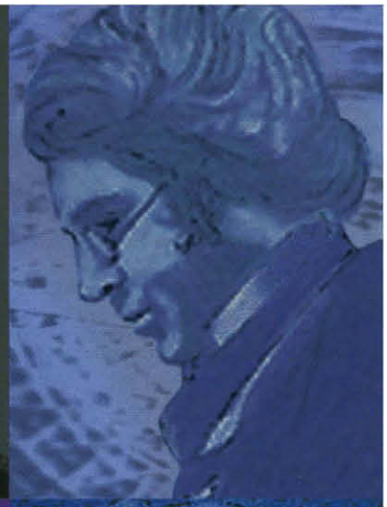

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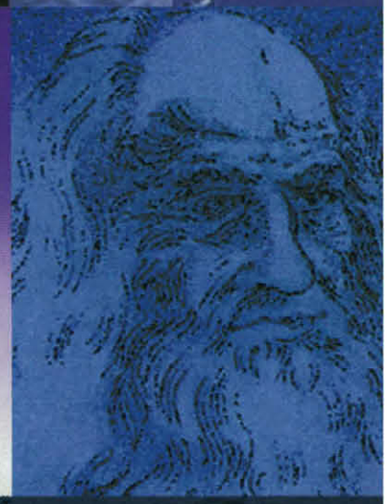

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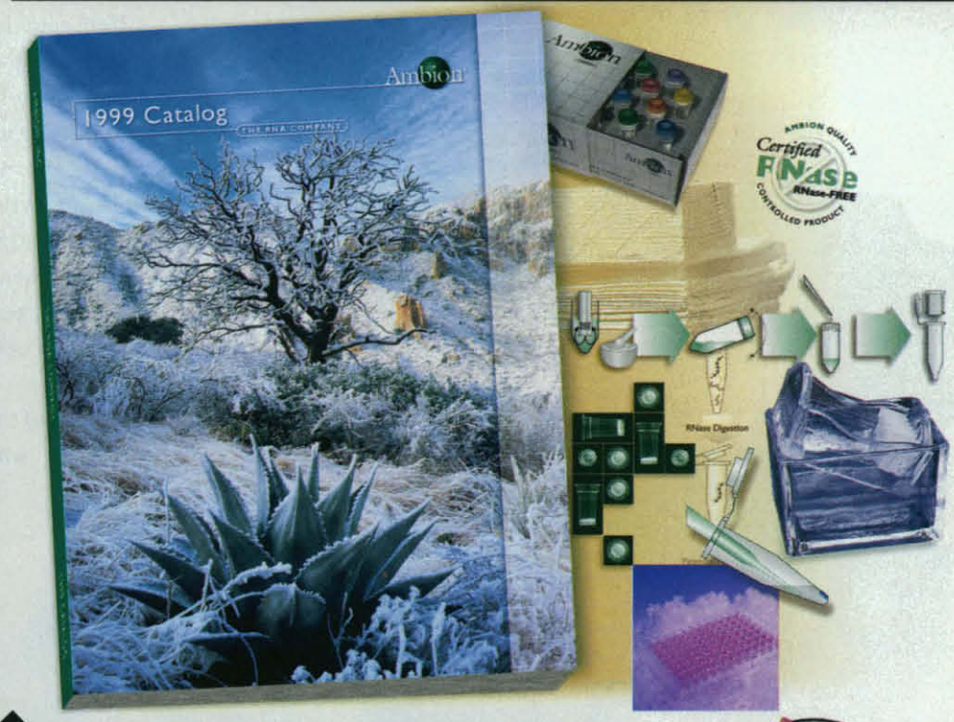

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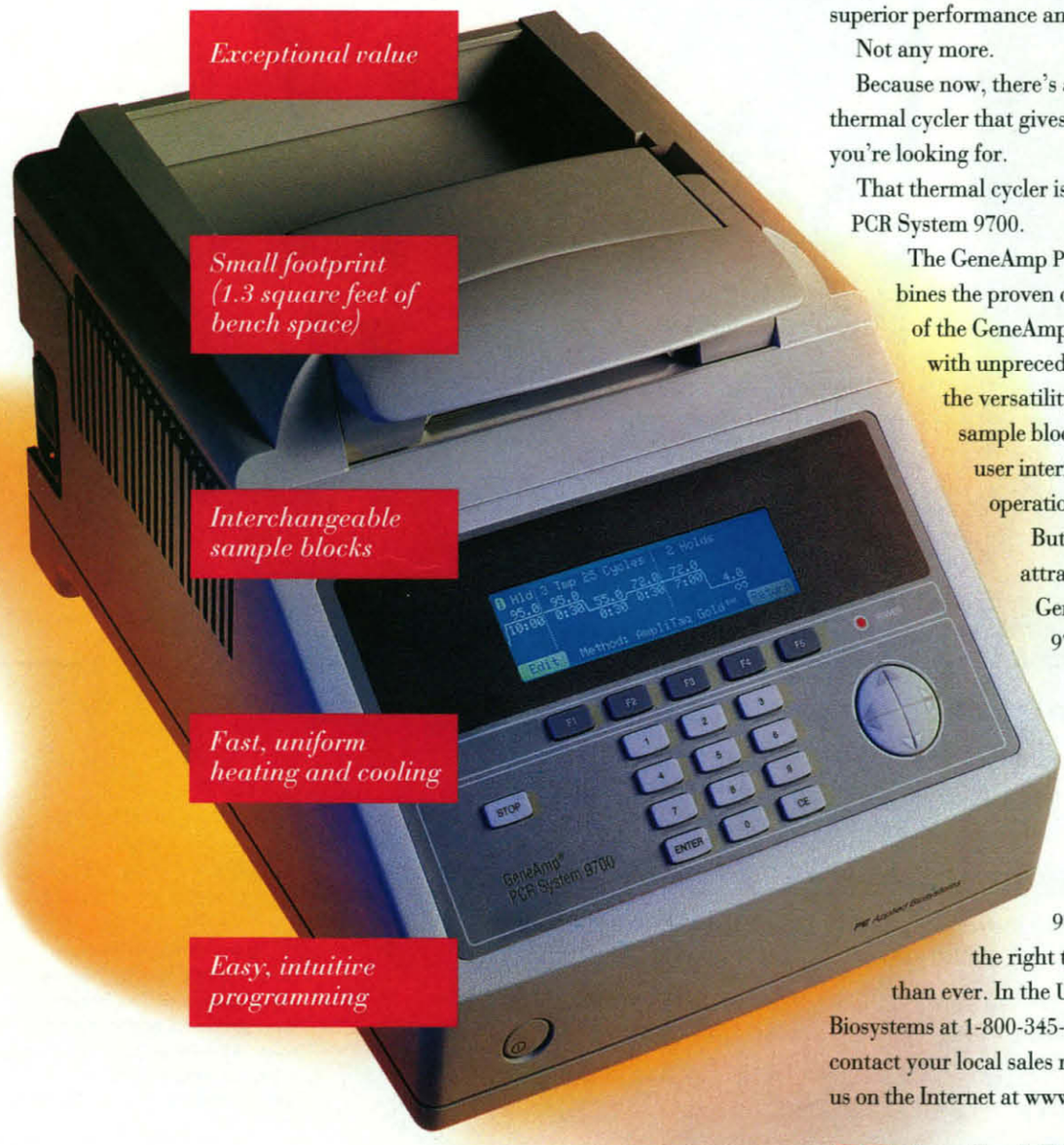

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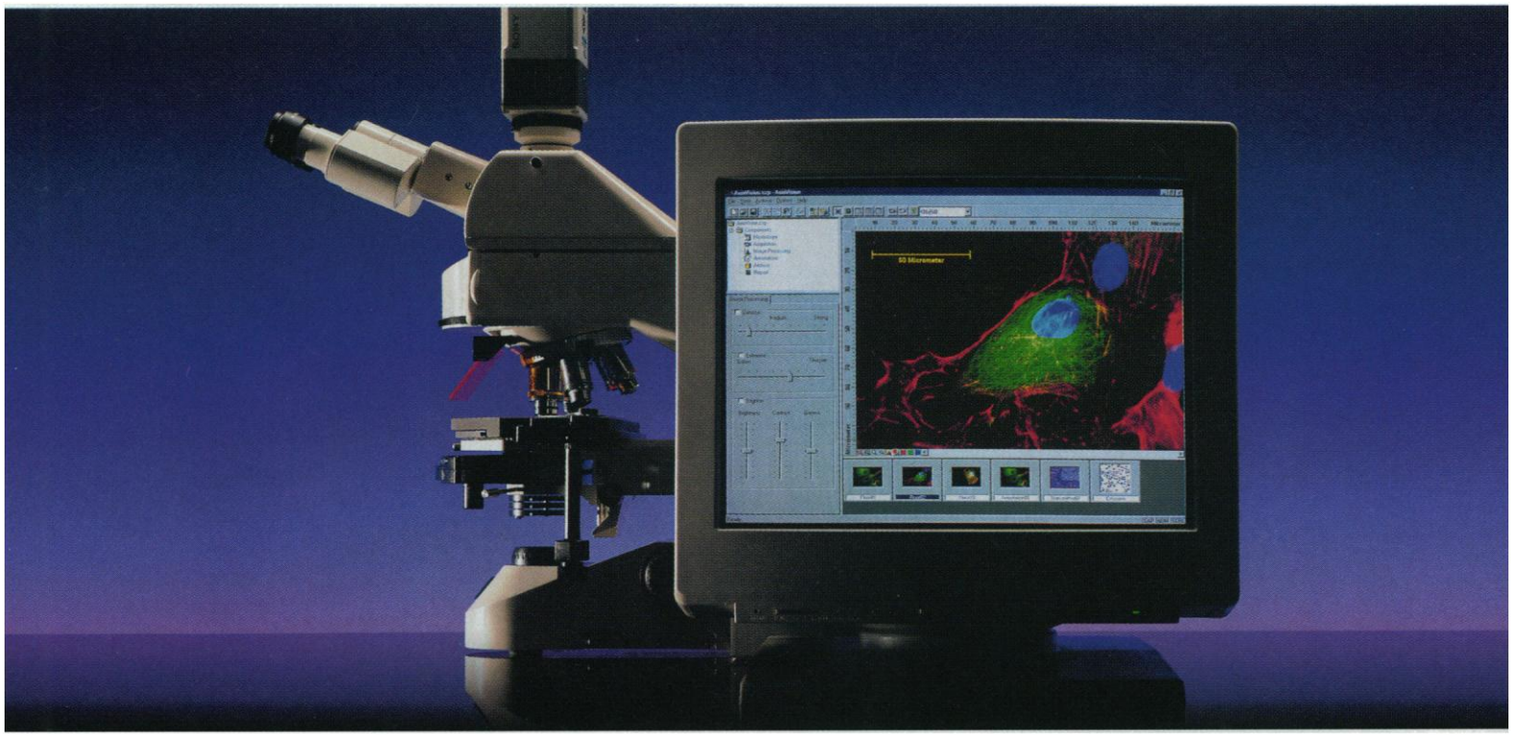

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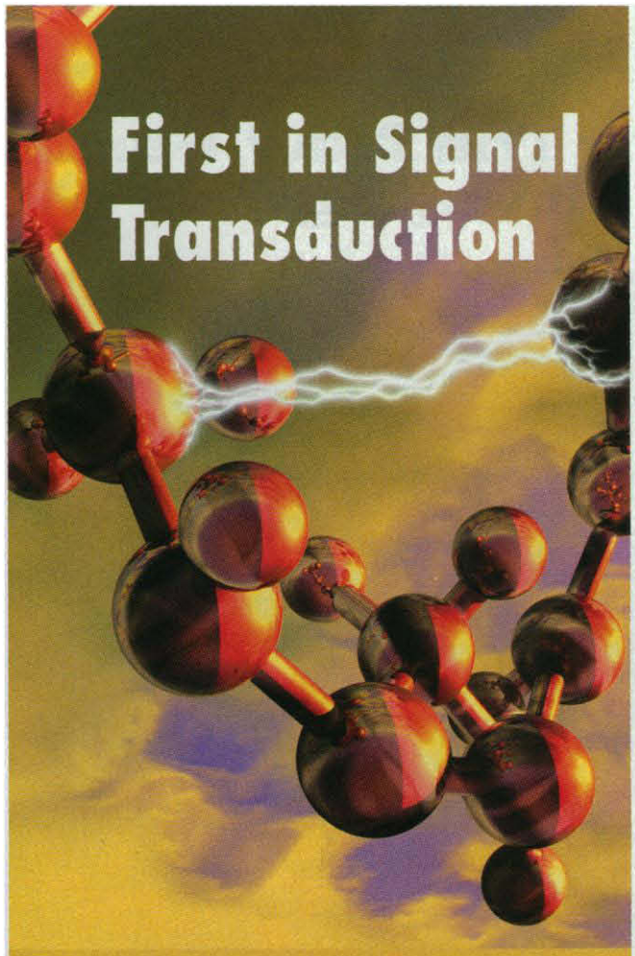

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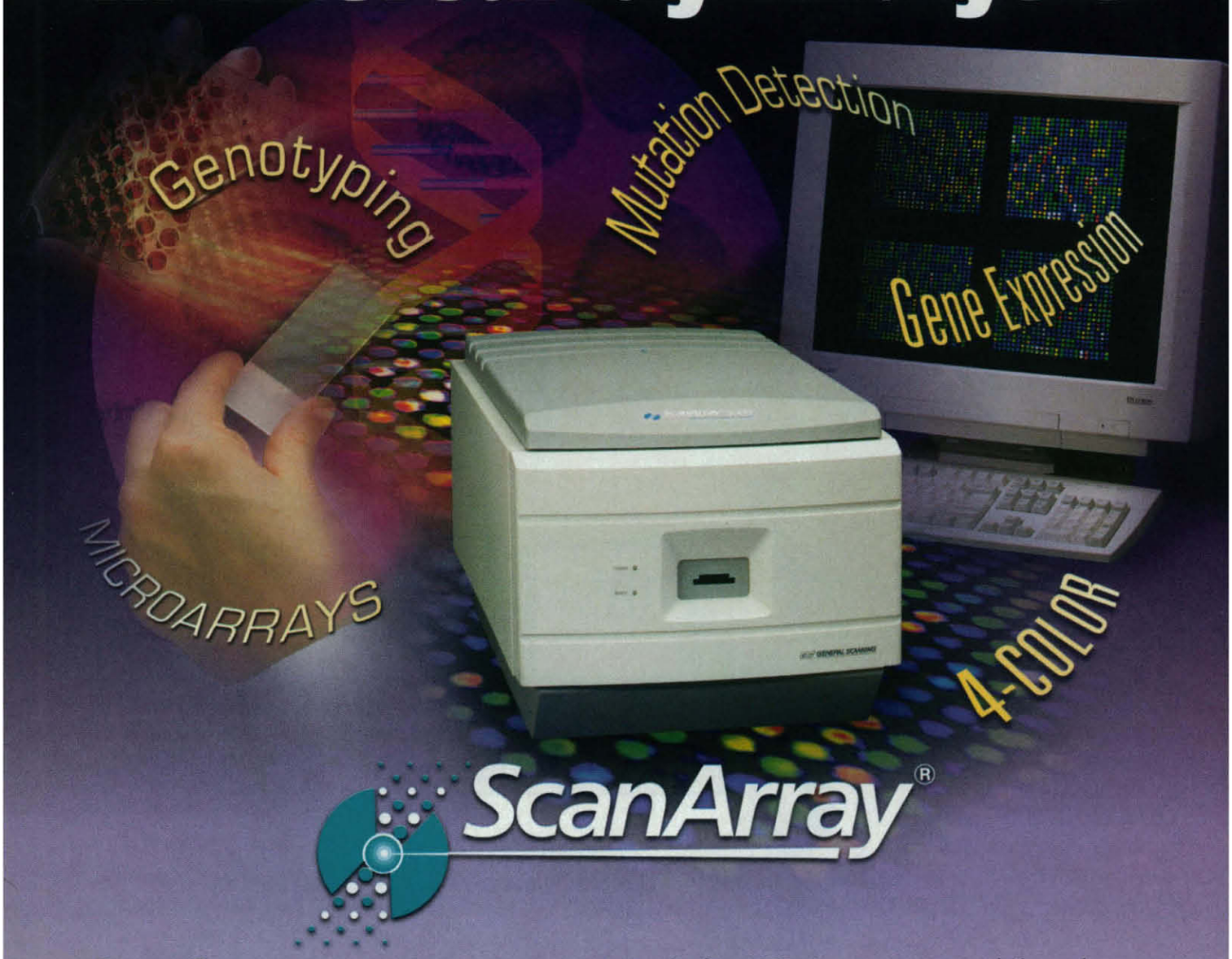

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